

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, C07K 14/47, A61K 38/17, C12Q 1/68, C12N 1/19, 1/21	A3	(11) International Publication Number: WO 99/28460 (43) International Publication Date: 10 June 1999 (10.06.99)
(21) International Application Number: PCT/NL98/00687 (22) International Filing Date: 3 December 1998 (03.12.98) (30) Priority Data: 97203781.6 3 December 1997 (03.12.97) EP (71) Applicant (for all designated States except US): LEADD B.V. [NL/NL]; Wassenaarseweg 72, NL-2333 AL Leiden (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): NOTEBORN, Mathieu, Hubertus, Maria [NL/NL]; Sternstraat 15, NL-2352 EH Leiden (NL). DANEN-VAN OORSCHOT, Astrid, Adriana, Anna, Maria [NL/NL]; Berliozplein 19, NL-2651 VG Berkel en Rodenrijs (NL). (74) Agent: OTTEVANGERS, S., U.; Vereenigde Octrooibureaux, Nieuwe Parklaan 97, NL-2587 BN The Hague (NL).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 12 August 1999 (12.08.99)	

(54) Title: MOLECULES INTERACTING WITH APOPTIN

(57) Abstract

The invention relates to activation of apoptosis by means of interference of Hou-like and/or IFP35-like compounds. Also the invention relates to anti-tumor therapies with compounds, which negatively interfere with Hou-like and/or IFP35-like compounds leading to induction of apoptosis, resulting in the elimination of tumor cells. Also the invention relates to therapies for diseases related to aberrant apoptosis induction, such as auto-immune disease. Also the invention describes the diagnosis of cells, which are susceptible to apoptin- or apoptin-like induced apoptosis.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P21694PC00	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/NL 98/ 00687	International filing date (day/month/year) 03/12/1998	(Earliest) Priority Date (day/month/year) 03/12/1997
Applicant LEADD B.V. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

MOLECULES INTERACTING WITH APOPTIN

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 17, in as far as it concerns an in vivo method, is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/ composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see continuation-sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

7, 13-15, 17 and 1-6, 9-12 partly

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 7,13-15,17 and 1-6,9-12 partly

Nmi/hou like proteins , their corresponding nucleic acids,
their use in hybridization and their vectors

2. Claims: 8,16 and 1-6,9-12 partly

IFP35 like proteins , their corresponding nucleic acids,
their use in hybridization and their vectors

3. Claim : 18

use of apoptin to find proteinaceous substances associated
with apoptosis

INTERNATIONAL SEARCH REPORT

International Application No

T/NL 98/00687

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/47 A61K38/17 C12Q1/68 C12N1/19
C12N1/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BAO J ET AL: "Isolation and characterization of Nmi, a novel partner of Myc proteins" ONCOGENE, 12 (10). 1996. 2171-2176., XP002064426 cited in the application see the whole document</p> <p>---</p> <p>-/--</p>	1-7,9-15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

29 March 1999

Date of mailing of the international search report

18.06.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gurdjian, D

INTERNATIONAL SEARCH REPORT

International Application No

CT/NL 98/00687

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ADAMS MD ET AL: "Rapid cDNA sequencing (expressed sequence tags) from a directionally cloned human infant brain cDNA library." NAT GENET, AUG 1993, 4 (4) P373-80, XP002064427 UNITED STATES see table EST60469	1-7,9-15
A	-& EMEst18 Databank Accession number AA352450 18-APR-1997 Adams M.D. et Al. XP002096573 see the whole document ---	1-7,9-15
A	EMEST16 DATABASE Accession number AA173501 Hillier L. et al. 27-DEC-1996 (Rel. 50, Created) similar to TR:G1322220 G1322220 HOU. XP002096574 see the whole document ---	1-7,9-15
A	ZHUANG S -M ET AL: "APOPTIN, A PROTEIN ENCODED BY CHICKEN ANEMIA VIRUS, INDUCES CELL DEATH IN VARIOUS HUMAN HEMATOLOGIC MALIGNANT CELLS IN VITRO" LEUKEMIA, vol. 9, no. SUPPL. 01, October 1995, pages S118-S120, XP000602147 cited in the application see the whole document ' ---	1-7,9-15
A	ZHUANG S -M ET AL: "APOPTIN, A PROTEIN DERIVED FROM CHICKEN ANEMIA VIRUS, INDUCES P53- INDEPENDENT APOPTOSIS IN HUMAN OSTEOSARCOMA CELLS" CANCER RESEARCH, vol. 55, no. 3, 1 February 1995, pages 486-489, XP000602162 cited in the application see the whole document ---	1-7,9-15
T	DE 196 28 894 A (HAGENMAIER HANS PAUL) 22 January 1998 see claims 1-14,16,17 -----	1,13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

T/NL 98/00687

Patent document
cited in search report

Publication
date

Patent family
member(s)

Publication
date

DE 19628894 A

22-01-1998

WO

9803676 A

29-01-1998

P.B.5818 - Patentlaan 2
2280 HV Rijswijk (ZH)
☎ (070) 3 40 20 40
TX 31651 epo nl
FAX (070) 3 40 30 16

Europäisches
Patentamt

Zweigstelle
in Den Haag
Recherchen-
abteilung

European
Patent Office

Branch at
The Hague
Search
division

Office européen
des brevets

Département à
La Haye
Division de la
recherche

mulders, Theodorus A.H.J., Ir.
Vereenigde Octrooibureaux
Nieuwe Parklaan 97
2587 BN 's-Gravenhage
PAYS-BAS

Datum/Date

21.09.1998

Zeichen/Ref./Réf.

Eur 4504

Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°.

97203781.6

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire

Leadd B.V.

COMMUNICATION

The European Patent Office herewith transmits

- ☐ the European search report
- ☐ the declaration under Rule 45 EPC
- ☒ the partial European search report under Rule 45 EPC
- ☐ the supplementary European search report concerning the international application under Article 157(2) EPC relating to the above-mentioned European patent application. Copies of the documents cited in the search report are enclosed.

The following specifications given by the applicant have been approved by the Search Division :

- ☒ Abstract ☐ Title ☐ Figure
 - ☐ The abstract was modified by the Search Division and the definitive text is attached to this communication.
 - ☐ The following figure will be published with the abstract, since the Search Division considers that it better characterises the invention than the one indicated by the applicant.
- Figure:
- ☐ Additional copy(copies) of the documents cited in the European search report.

REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.



EPO F rm 1507 02.93



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 97 20 3781
shall be considered, for the purposes of subsequent
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	BAO J ET AL: "Isolation and characterization of Nmi, a novel partner of Myc proteins" ONCOGENE, 12 (10). 1996. 2171-2176., XP002064426 * the whole document *	1-7,9-15	C12N15/12 C07K14/47 A61K38/17 C12Q1/68 C12N1/19 C12N1/21
A	ADAMS MD ET AL: "Rapid cDNA sequencing (expressed sequence tags) from a directionally cloned human infant brain cDNA library." NAT GENET, AUG 1993, 4 (4) P373-80, XP002064427 UNITED STATES * table EST60469 *	1-7,9-15	
A	& EMBL databank Accession number AA352450 18-APR-1997 * the whole document *	1-7,9-15	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			C07K C12N
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>Although claim 17, in as far it concerns an in vivo method, is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.</p>			
Place of search		Date of completion of the search	Examiner
THE HAGUE		15 May 1998	Gurdjian, D
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

4
EPO FORM 1503 03 82 (P04C07)



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 97 20 3781

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	ZHUANG S -M ET AL: "APOPTIN, A PROTEIN ENCODED BY CHICKEN ANEMIA VIRUS, INDUCES CELL DEATH IN VARIOUS HUMAN HEMATOLOGIC MALIGNANT CELLS IN VITRO" LEUKEMIA, vol. 9, no. SUPPL. 01, October 1995, pages S118-S120, XP000602147 * the whole document * ---	1-7,9-15	
A	ZHUANG S -M ET AL: "APOPTIN, A PROTEIN DERIVED FROM CHICKEN ANEMIA VIRUS, INDUCES P53- INDEPENDENT APOPTOSIS IN HUMAN OSTEOSARCOMA CELLS" CANCER RESEARCH, vol. 55, no. 3, 1 February 1995, pages 486-489, XP000602162 * the whole document * ---	1-7,9-15	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
T	DE 196 28 894 A (HAGENMAIER HANS PAUL) 22 January 1998 * claims 1-14,16,17 * -----	1,13	



European Patent
Office

Application Number
EP 97 20 3781

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

Claims: 7,13-15,17 and 1-6,9-12 partly



European Patent
Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 97 20 3781

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 7,13-15,17 and 1-6,9-12 partly

Nmi/hou like proteins , their corresponding nucleic acids,
their use in hybridization and their vectors

2. Claims: 8,16 and 1-6,9-12 partly

IFP35 like proteins , their corresponding nucleic acids,
their use in hybridization and their vectors

3. Claim : 18

use of apoptin to find proteinaceous substances associated
with apoptosis

EP 97 20 3781

15-05-1998

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19628894 A	22-01-1998	WO 9803676 A	29-01-1998

8.
H 03.12.97

25

CLAIMS

1. A recombinant and/or isolated nucleic acid molecule encoding at least a functional part of a member of the family of Nmi-like proteins or at least a functional part of a member of the family of Hou-like proteins or at least a functional part of a member of the family of IFP35-like proteins for use in the induction of apoptosis in a population of cells related to a pathological condition.
2. A use according to claim 1 wherein said nucleic acid molecule comprises at least a functional and specific part of the sequence of figure 1, 2, 4 or 5 or encoding an amino sequence of figure 6 or a sequence at least 60, preferably 70, preferably 90 % homologous with said functional and specific sequence or comprising a sequence hybridizing to any of the foregoing sequences under stringent conditions.
3. Use according to claim 1 or 2 wherein said nucleic acid comprises an expression vector.
4. Use according to anyone of the foregoing claims whereby said cells are provided with apoptosis inducing activity.
5. Use according to claim 4 whereby said apoptosis inducing activity is apoptin-like activity.
6. Use according to any of claims 1-5 wherein said nucleic acid is part of a gene delivery vehicle.
7. A recombinant and/or isolated nucleic acid molecule encoding an Nmi/Hou-like protein comprising at least a functional and/or specific part of the sequence of figure 1 or figure 2 or a sequence at least 60, preferably 70, more preferably 80% homologous therewith.
8. A recombinant and/or isolated nucleic acid molecule encoding an IFP35-like protein comprising at least a functional and/or specific part of the sequence of figure 4 or figure 5 or encoding at least a functional and/or specific part of the amino acid sequence of figure 6 or a sequence at least 60, preferably 70, more preferably 80% homologous therewith.

9. An expression vector comprising a recombinant nucleic acid molecule according to claim 7 and/or 8.
10. An expression vector according to claim 9 further comprising a sequence encoding apoptotic activity.
- 5 11. An expression vector according to claim 10 wherein said sequence encoding apoptotic activity encodes apoptin or a functional fragment and/or equivalent thereof.
12. A gene delivery vehicle comprising a recombinant nucleic acid molecule according to claim 7 or 8 or an expression
10 vector according to anyone of claims 9-11.
13. A recombinant or isolated proteinaceous substance comprising at least a functional part of a member of the family of Nmi/Hou-like proteins or at least a functional part of a member of the family of Hou-like proteins for use
15 in the induction of apoptosis in a population of cells related to a pathological condition.
14. An Nmi/Hou-like proteinaceous substance having at least a functional and/or specific part of the sequence of figure 3 or being encoded by a functional and/or specific part of the
20 sequence of figure 1 or figure 2 or being at least 60, preferably 70, preferably 80% homologous to at least a functional and/or specific part of the sequence of figure 3 or being at least 60, preferably 70, preferably 80% homologous to a protein encoded by at least a functional
25 and/or specific part of the sequence of figure 1 or figure 2.
15. A recombinant or isolated proteinaceous substance comprising at least a functional part of a member of the family of Nmi/Hou-like proteins or at least a functional part of a member of the family of Hou-like proteins for use
30 in the induction of apoptosis in a population of cells related to a pathological condition.
16. An IFP35-like proteinaceous substance having at least a functional and/or specific part of the sequence of figure 6 or 7 or being encoded by a functional and/or specific part of
35 the sequence of figure 4 or figure 5 or being at least 60, preferably 70, preferably 80% homologous to at least a

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

OTTEVANGERS, S., U.
Vereenigde
Nieuwe Parklaan 97
NL-2587 BN The Hague
PAYS-BAS

Date of mailing (day/month/year) 14 April 2000 (14.04.00)	
Applicant's or agent's file reference P21694PC00	IMPORTANT NOTIFICATION
International application No. PCT/NL98/00687	International filing date (day/month/year) 03 December 1998 (03.12.98)

1. The following indications appeared on record concerning: <input type="checkbox"/> the applicant <input type="checkbox"/> the inventor <input checked="" type="checkbox"/> the agent <input type="checkbox"/> the common representative		
Name and Address OTTEVANGERS, S., U. Vereenigde Octrooibureaux Nieuwe Parklaan 97 NL-2587 BN The Hague Netherlands	State of Nationality	State of Residence
	Telephone No. 070 4166 711	
	Facsimile No. 070 4166 799	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: <input type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence		
Name and Address OTTEVANGERS, S., U. Vereenigde Nieuwe Parklaan 97 NL-2587 BN The Hague Netherlands	State of Nationality	State of Residence
	Telephone No. 070 4166 711	
	Facsimile No. 070 4166 799	
	Teleprinter No.	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to: <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input type="checkbox"/> the International Preliminary Examining Authority </div> <div> <input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other: </div> </div>		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Marie-José Devillard Telephone No.: (41-22) 338.83.38
--	---



PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 August 1999 (19.08.99)	
International application No. PCT/NL98/00687	Applicant's or agent's file reference P21694PC00
International filing date (day/month/year) 03 December 1998 (03.12.98)	Priority date (day/month/year) 03 December 1997 (03.12.97)
Applicant NOTEBORN, Mathieu, Hubertus, Maria et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
29 June 1999 (29.06.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer A. Karkachi</p> <p>Telephone No.: (41-22) 338.83.38</p>
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P21694PC00	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/NL98/00687	International filing date (day/month/year) 03/12/1998	Priority date (day/month/year) 03/12/1997
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant LEADD B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 29/06/1999	Date of completion of this report 07.03.00
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stolz, B  Telephone No. +49 89 2399 8416

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL98/00687

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-27 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 8, 16, 18, and 1 to 6, 17 partially.

because:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL98/00687

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. cf. above.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 1-7, 9-15
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-7, 9-15
Industrial applicability (IA)	Yes:	Claims 1-7, 9-15
	No:	Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL98/00687

1. Reasoned statement

1.1. The application describes the isolation and function of proteins, termed "Nmi/Hou like". The proteins function somewhere along the apoptin inducible apoptosis pathway. Claimed are nucleic acid molecules, proteins, and the use of these for the induction of apoptosis.

1.2. Novelty (Art. 33(2) PCT)

The type of claims 1 to 6, and 13, i.e. product or process claims, is not entirely clear. Claim 1 is directed to a recombinant protein, yet comprises features typical of a process claim ("for use in ..."). For the present analysis, and in line with the standard interpretation of claims, it is assumed to refer to a recombinant protein "suitable for use in ...". The same is true for claims 2 to 6, and 13.

The following two documents affect novelty of claims 1 to 7, and 9 to 15:

- D1: BAO J ET AL: 'Isolation and characterization of Nmi, a novel partner of Myc proteins' ONCOGENE, 12 (10). 1996. 2171-2176., XP002064426 cited in the application
- D2: EMBEST16 DATABASE Accession number AA173501 Hillier L. et al. 27-DEC-1996 (Rel. 50, Created) similar to TR:G1322220 G1322220 HOU. XP002096574

D1 describes the cloning and expression of Nmi, clearly a member of the family of Nmi/Hou like proteins. Moreover, this molecule is more than 90% identical to the molecule encoded by Figs. 1 and 2. This takes away the novelty of any claim directed to nucleic acid molecules encoding at least a part of a member of the family of Nmi-like proteins or to partially homologous or hybridizing molecules. Likewise, the novelty of the claims to proteinaceous substances is affected.

D2 describes an EST displaying 97% sequence identity in a 290 bp overlap with the sequence of Fig. 2 (Seq. ID no. 5) of the present application. This represents certainly a molecule comprising "at least a specific part" of the sequence of Fig. 2 according to claim 7. In the absence of any demonstration of an association of

specific functions (what functions?) with specific parts of the identified molecules, it cannot be ruled out that this document also affects the novelty of claims 1 to 6.

2. Certain observations

- 2.1. The claims contain a number of terms which are ambiguous or open to interpretation and as such render the scope of the claims unclear.

Many claims refer to molecules encoding or having "at least a functional part of a member of the family of Nmi/Hou-like proteins". The application provides no information on any function of the identified proteins apart from the capability of inducing apoptosis. The situation is complicated by the definition of Nmi-like activity on p. 4 of the description which includes molecules with "similar" functions. Therefore, the reference to at least a (unspecified) function is unclear. The term "Nmi-like protein" is unclear because its extent is undefined. The person of skill is not in a position to distinguish Nmi-like proteins from non-like proteins. This argument applies also to the apoptin-like proteins of claim 17. Furthermore, not all members of the claimed family of proteins are known. Consequently, not all their functions and functional parts can be known.

For the same reason, a broadening of the scope of the claims by reference to sequences homologous to unspecified members of the family of Nmi/hou-like DNAs or proteins is not possible.

The term "a specific part" is completely undefined and hence open to interpretation.

The reference to "a population of cells related to a pathological condition" is also unclear. Are these cells themselves in a pathological condition, or are they in a particular relation with such cells?